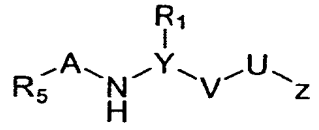
Patent claims

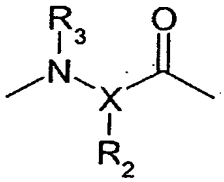
1. A compound of the general formula I



(I)

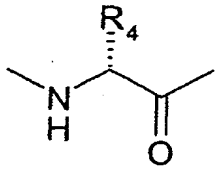
wherein

A is $P_2 - P_1$ in which



P_1 =

and



P_2 = ;

R_1 is H or $-(CH_2)_aCOOR_6$, in which a = 0, 1, 2, 3, 4 or 5, preferably in which a = 0, 1 or 2, where R_6 is a branched or unbranched alkyl radical preferably having from 1 to 6 C atoms, in particular from 1 to 3 C atoms, especially ethyl;

R_2 is an H, a branched or unbranched alkyl radical having from 1 to 8 C atoms, preferably having from 1 to 3 C atoms, or

$-(CH_2)_cCOOR_8$, in which c = 1, 2, 3 or 4, where R_8 is H or a branched or unbranched alkyl radical preferably having from 1 to 6 C atoms, in particular from 1 to 3 C atoms, especially ethyl, or

$-(CH_2)_d-OR_9$, in which d = 1, 2, 3 or 4, where R_9 is H, or

$-(CH_2)_eR_{10}$, $-(CH_2)_e-OR_{10}$, $-(CH_2)_e-SR_{10}$, $-(CH_2)_e$-guanidino, $-(CH_2)_e$-imidazole or $-(CH_2)_eNHR_{10}$, in which e = 1, 2, 3, 4 or 5, where R_{10} is H, a branched or unbranched alkyl radical having 1-16, in particular 1-8, especially 1-3, C atoms, or a substituted or unsubstituted aryl, heteroaryl, aralkyl or heteroaralkyl radical, where the alkyl radical preferably possesses from 1 to 16, in particular from 1 to 8, especially from 1 to 3, C atoms, and the aryl or heteroaryl radical preferably possesses from 4 to 14, in particular from 6 to 10, especially 6 C atoms, and preferably from 1 to 3 N as heteroatom, or

$-(CH_2)_kO-CO-OR_{16}$, in which k = 1, 2, 3, 4, 5, 6, 7 or 8, where R_{16} is a branched or unbranched alkyl having 1-16, preferably 1-8, in particular 1-4, especially 1-2, C atoms, a substituted or unsubstituted aryl, heteroaryl, aralkyl or heteroaralkyl radical, or an adamantyl, a camphor or a cyclohexylmethyl radical, preferably benzyl; and

R_5 is $-(CH_2)_g(CH_3)_h$, $-(CH_2)_i$-aryl, in which g + h = i = 0, 1, 2 or 3, $-SO_2R_{12}$, $-COR_{12}$ or $-COOR_{12}$, where R_{12} is a branched or unbranched alkyl having 1-16, preferably 1 to 8, in particular 1 to 4, especially 1 to 2, C atoms, a substituted or unsubstituted aryl, heteroaryl, aralkyl or heteroaralkyl radical, or an adamantyl, a camphor or a cyclohexylmethyl radical,

preferably benzyl, where R_5 is modified with a charged or uncharged group, preferably a $-(CH_2)_jCOOR_{13}$, $-(CH_2)_jSO_2R_{13}$, $-(CH_2)_jNH_2$, $-(CH_2)_j$-amidino, $-(CH_2)_j$-hydroxyamidino or $-(CH_2)_j$-guanidino group in which j = 0, 1 or 2, where R_{13} is H or an alkyl radical preferably having from 1 to 6 C atoms, in particular ethyl; or

R_2 is $-(CH_2)_cCOOR_8$, in which c = 1, 2, 3 or 4, where R_8 is H or a branched or unbranched alkyl radical preferably having from 1 to 6 C atoms, in particular from 1 to 3 C atoms, especially ethyl, or
$-(CH_2)_e-SR_{10}$, $-(CH_2)_e$-guanidino, $-(CH_2)_e$-imidazole or $-(CH_2)_eNHR_{10}$, in which e = 1, 2, 3, 4 or 5, where R_{10} is H, a branched or unbranched alkyl radical having 1-16, in particular 1-8, especially 1-3, C atoms, or a substituted or unsubstituted aryl, heteroaryl, aralkyl or heteroaralkyl radical, where the alkyl radical preferably possesses from 1 to 16, in particular from 1 to 8, especially from 1 to 3, C atoms, and the aryl or heteroaryl radical preferably possesses from 4 to 14, in particular from 6 to 10, especially 6 C atoms, and preferably from 1 to 3 N as heteroatom, or
$-(CH_2)_kO-CO-OR_{16}$, in which k = 1, 2, 3, 4, 5, 6, 7 or 8, where R_{16} is a branched or unbranched alkyl having 1-16, preferably 1-8, in particular 1-4, especially 1-2, C atoms, a substituted or unsubstituted aryl, heteroaryl, aralkyl or heteroaralkyl radical, or an adamantyl, a camphor or a cyclohexylmethyl radical, preferably benzyl; and

R_5 is $-(CH_2)_g(CH_3)_h$, $-(CH_2)_i$-aryl, in which g + h = i = 0, 1, 2 or 3, $-SO_2R_{12}$, $-COR_{12}$ or $-COOR_{12}$, where R_{12} is a branched or unbranched alkyl having 1-

16, preferably 1 to 8, in particular 1 to 4, especially 1 to 2, C atoms, a substituted or unsubstituted aryl, heteroaryl, aralkyl or heteroaralkyl radical, or an adamantyl, a camphor or a cyclohexylmethyl radical, preferably benzyl, where R_5 is modified with a charged or uncharged group, preferably a $-(CH_2)_jCOOR_{13}$, $-(CH_2)_jSO_2R_{13}$, $-(CH_2)_jNH_2$, $-(CH_2)_j$-amidino, $-(CH_2)_j$-hydroxyamidino or $-(CH_2)_j$-guanidino group in which j = 0, 1 or 2, where R_{13} is H or an alkyl radical preferably having from 1 to 6 C atoms, in particular ethyl;

R_3 is H or $-(CH_2)_bR_7$, in which b = 1, 2, 3, 4, 5, 6, 7 or 8, preferably in which b = 2 or 3, where R_7 is H, a branched or unbranched alkyl radical having from 1 to 10 C atoms, preferably having from 1 to 3 C atoms, or a charged radical, preferably a $-(CH_2)_jCOOR_{13}$, $-(CH_2)_jSO_2R_{13}$, or $-(CH_2)_jNH_2$, or $-(CH_2)_j$-amidino, $-(CH_2)_j$-hydroxyamidino or $-(CH_2)_j$-guanidino group in which j = 0, 1 or 2, where R_{13} is H or an alkyl radical preferably having from 1 to 6 C atoms, in particular from 1 to 4, especially ethyl, and with P_1 being present in the L configuration in the structure A;

R_4 is a branched or unbranched alkyl radical having from 1 to 8, preferably from 1 to 3, C atoms, $-(CH_2)_fOR_{11}$, $-(CH_2)_fSR_{11}$, or $-(CH_2)_fNHR_{11}$ in which f = 1, 2, 3, 4, 5, 6, 7 or 8, where R_{11} is H or $-CO-OR_{17}$, where R_{17} is a branched or unbranched alkyl having 1-16, preferably 1-8, in particular 1-4, especially 1-2, C atoms, a substituted or unsubstituted aryl, heteroaryl, aralkyl or heteroaralkyl radical, or an adamantyl, a camphor or a cyclohexylmethyl radical, preferably benzyl, and with P_2 being

present in the D configuration in the structure A;

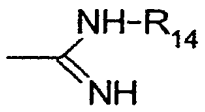
U is a phenyl or cyclohexyl radical or a heterophenyl or heterocyclohexyl radical preferably having at least one N, S or O as heteroatom, in particular pyridine, piperidine or pyrimidine;

V is $(CH_2)_n$ in which n is 0, 1, 2 or 3, preferably 0;

X is N or CH, preferably CH;

Y is N or $(CH)_m$ in which m = 0 or 1, preferably CH;

Z occurs in the 3 or 4 position and is an aminomethyl, a guanidino or an amidino group



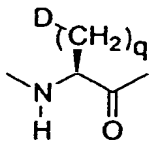
where R_{14} is H, OH, NH_2, $-COR_{15}$ or $-COOR_{15}$, where R_{15} is a branched or unbranched alkyl radical having from 1 to 16, preferably from 1 to 8, in particular from 1 to 4, especially from 1 to 2, C atoms or a substituted or unsubstituted aryl or heteroaryl, aralkyl or heteroaralkyl radical, where the alkyl radical preferably possesses from 1 to 16, in particular from 1 to 8, especially from 1 to 4, and particularly preferably from 1 to 2, C atoms and the aryl or heteroaryl radical preferably possesses from 4 to 14, in particular from 6 to 10, especially 6, C atoms and, preferably, from 1 to 3 N as heteroatom;

characterized in that one or more charged radicals, preferably derived from -COOH, $-CH(COOH)_2$, $-SO_2H$, NH_2, an amidino, hydroxyamidino, amidrazono or guanidino group, is/are present in the radicals R_1, R_2, R_3 or R_5;

or a compound of the general formula I in the form of a prodrug or in the form of its salt.

2. A compound as claimed in claim 1, in which an amino group-functionalized or carboxyl group-functionalized oligo- or polyalkylene glycol chain, in particular a poly- or oligoethylene glycol chain or poly- or oligopropylene glycol chain, is coupled directly to a functional group of R_2, in particular by way of an -NH or a -CO group, with the formation of an amide bond at R_2, with the oligo- or polyalkylene glycol chain possessing a functional group, in particular a substituted or unsubstituted amino group and/or carboxyl group, at least at both ends, or with the oligo- or polyalkylene glycol chain possessing a functional group, in particular a substituted or unsubstituted amino group and/or carboxyl group, at one end and being present, at the other end, as an alkyl ether having 1-4 C atoms, in particular as methyl ether,
with R_2 preferably being
(a) $-(CH_2)_n-NH_2$ in which n is 1-5, preferably 4, or
(b) $-(CH_2)_n-COOH$ in which n is 1-5, preferably 1-3.

3. A compound as claimed in claim 1, wherein, after coupling the oligo- or polyalkylene glycol, P_1 has the general formula II



(II),

where q is 0, 1, 2, 3, 4 or 5 and D is formula III

E - F - G - (III)

where, when E is an H_2N, HOOC-$(CH_2)_n$-CO-NH, HOOC or H_2N-$(CH_2)_n$-NH-CO group, F is an oligo- or polyalkylene glycol of the general formula -$(CH_2)_d$-[O-CH_2-CH_2]$_v$O-$(CH_2)_m$-(NH-CO-CH_2-O-CH_2)$_k$- or -$(CH_2)_d$-[O-CH(CH_3)-CH_2]$_v$O-$(CH_2)_m$-(NH-CO-CH_2-O-CH_2)$_k$-, in which d = 1, 2, 3 or 4, v = an integer from 1 to 1000, preferably from 2 to 250, m = 0, 1, 2, 3 or 4, and k = 0 or 1, or, when E is a CH_3-O group, F is an oligo- or polyalkylene glycol chain of the general formula -$(CH_2)_d$-[O-CH_2-CH_2]$_v$O-$(CH_2)_m$-(NH-CO-CH_2-O-CH_2)$_k$- or -$(CH_2)_d$-[O-CH(CH_3)-CH_2]$_v$-O-$(CH_2)_m$-(NH-CO-CH_2-O-CH_2)$_k$-, in which d = 1, 2, 3 or 4, v = an integer from 1 to 1000, preferably from 1 to 250, m = 0, 1, 2, 3 or 4, and k = 0 or 1;
and G is -CO-NH- or -NH-CO-.

4. A compound as claimed in claim 1, wherein U is substituted at 1, 2 or 3 positions, preferably by a halogen, in particular fluorine or chlorine, or a methyl, ethyl, propyl, methoxy, ethoxy or propoxy radical.

5. A compound as claimed in claim 1, wherein a carboxyl group is protected as an ester, preferably as an ethyl ester.

6. A compound as claimed in claim 1 , in the form of a prodrug, with R_9 and/or R_{11} in this case being an

alkylcarbonyl, aralkylcarbonyl, alkyloxycarbonyl or aralkoxycarbonyl radical, with the alkyl radical preferably having from 1 to 6, in particular from 1 to 4, C atoms and the aryl radical preferably having from 5 to 8, in particular 6, C atoms.

7. A compound as claimed in claim 1, characterized in that the amidino group is in the 4 position in the amidinobenzylamide radical and in that P_2 is derived from the amino acid D-Ser and P_1 is derived from glycine, alanine, serine, aspartic acid or glutamic acid, and in that R_5 is an unsubstituted aryl- or aralkylsulfonyl radical, or such a radical provided with a carboxyl group or carboxyalkyl group, having from 1 to 16, preferably from 1 to 8, in particular from 1 to 4, especially from 1 to 2, C atoms in the alkyl radical and from 6 to 14, preferably from 6 to 10, in particular 6, C atoms in the aryl radical.

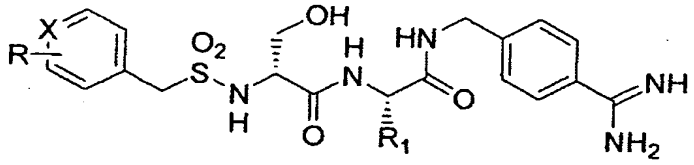
8. A compound as claimed in claim 1, characterized in that the amidino group is in the 4 position in the amidinobenzylamide radical and in that P_2 is the amino acid D-Ser and P_1 is a natural or artificial, unsubstituted or substituted, basic amino acid in the L configuration, for example Lys, homoLys, Arg, norArg, homoArg, His, Orn, Orn(2-imidazolinyl), Dab, 4-[(2-amino)pyrimidinyl]butyric acid, Dap, Ala[3-(2-pyrrolidinyl)], Ala[3-pyrrolidinyl-(2-N-amidino)], Ala[3-(N-piperazine-4-N-amidino], Ala(4-Pip), Ala[4-Pip(N-amidino)], homoAla(4-Pip), Ala[3-Pip-(N-amidino)], homoAla(3-Pip), homoAla[4-Pip(N-amidino)], Ala-(3-guanidino), Phe(3-amidino), Phe(4-amidino), Phe(3-NH_2), Phe(4-NH_2), Phe(3-guanidino), Phe(4-guanidino), Phe[4-(2-imidazolinyl)], Phe[3-CH_2-(guanidino)], Phe[4-CH_2-

(guanidino)], homoPhe(3-amidino), homoPhe(4-amidino), hPhe(3-NH_2), hPhe(4-NH_2), hPhe(3-guanidino), hPhe(4-guanidino), cis-Cha(4-NH_2), trans-Cha(4-NH_2), cis-homoCha(4-NH_2), trans-homoCha(4-NH_2), trans-Cha(4-CH_2NH_2) and trans-homoCha(4-CH_2NH_2), and in that R_5 is a sulfonyl group-provided aryl- or aralkylsulfonyl radical having from 1 to 16, preferably from 1 to 8, in particular from 1 to 4, especially from 1 to 2, C atoms in the alkyl radical and from 6 to 14, preferably from 6 to 10, in particular 6, C atoms in the aryl radical, which is bonded to the amino group of the D-Ser.

9. A compound as claimed in claim 8, characterized in that P_1 is the amino acid Lys or Arg.

10. A compound as claimed in claim 1 , characterized in that the substituent on the substituted aryl, heteroaryl, aralkyl or heteroaralkyl radical is a halogen, preferably fluorine, chlorine or bromine, in particular fluorine or chlorine.

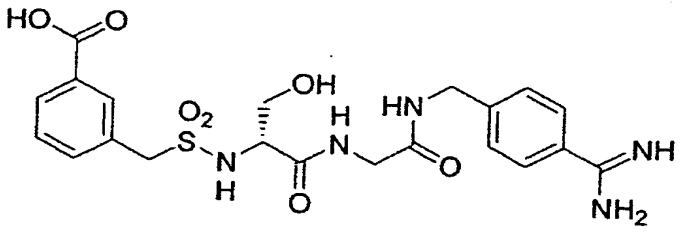
11. A compound as claimed in claim 1 , characterized in that a compound of the general formula I has the following structure:



in which R is COOH, HOOC-$(CH_2)_p$- or R_{18}OOC-$(CH_2)_p$- in which p = 1 and 2 and R_{18} = methyl or ethyl, or COOMe in ortho, meta or para, or H, and X is CH and R_1 is H; or

R is 4-COOH or 3-COOH, with X being CH and R_1 being H, CH_3 or CH_2-OH; or
R is 4-CN, with X being CH and R_1 being CH_3; or
R is 4-(NH_2-CH_2), with X being CH and R_1 being H; or
R is 4-COOMe, with X being CH and R_1 being CH_2-OH.

12. A compound as claimed in claim 1 , characterized in that a compound of the general formula I has one of the following structures:



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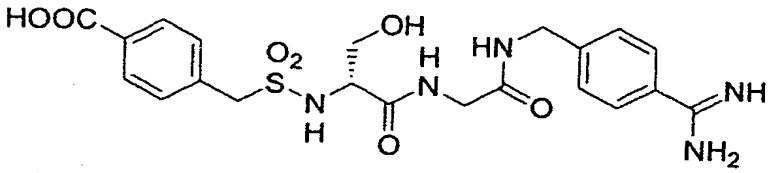

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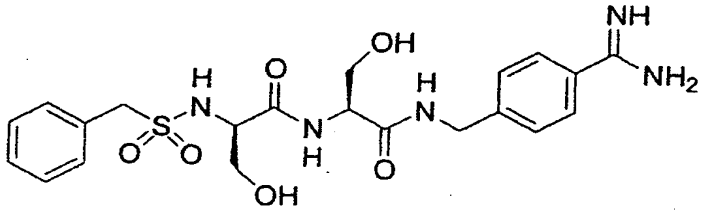

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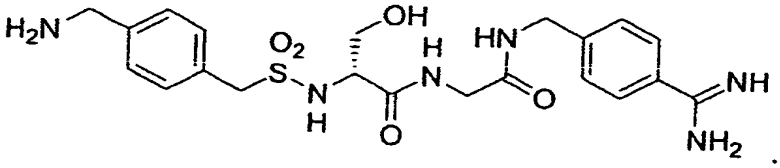
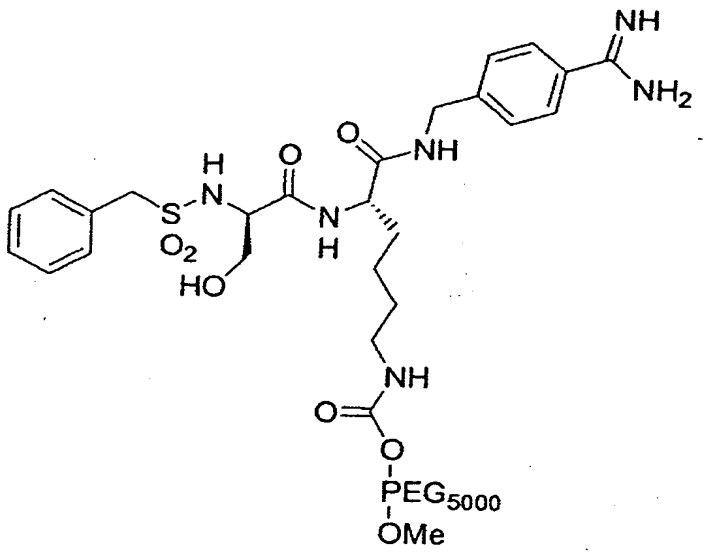


13. A compound as claimed in claim 1 , characterized in that a compound of the general formula I has one of the following structures:



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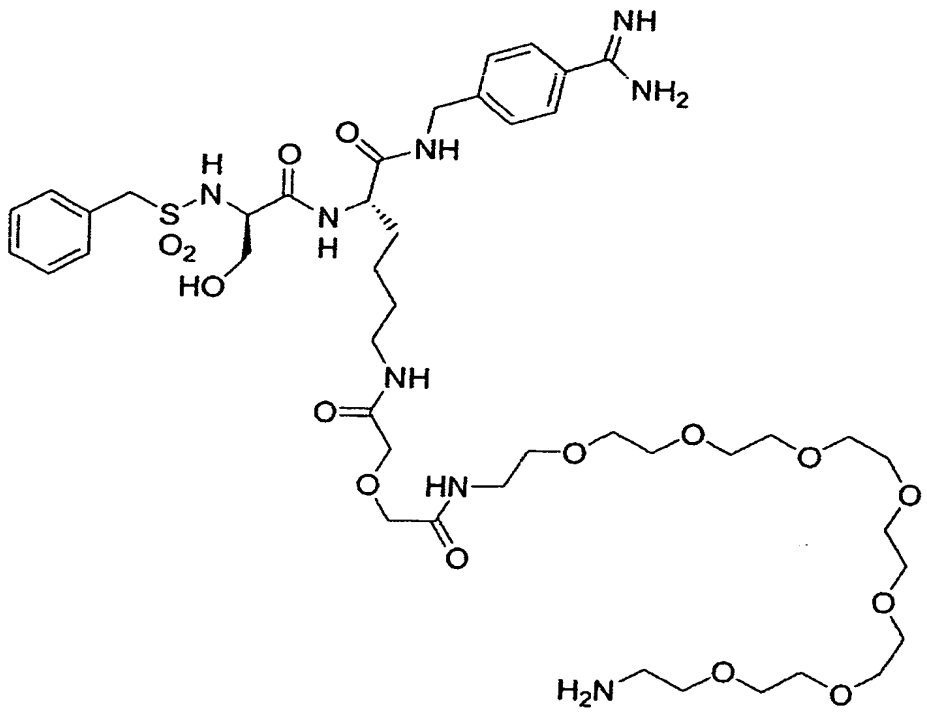

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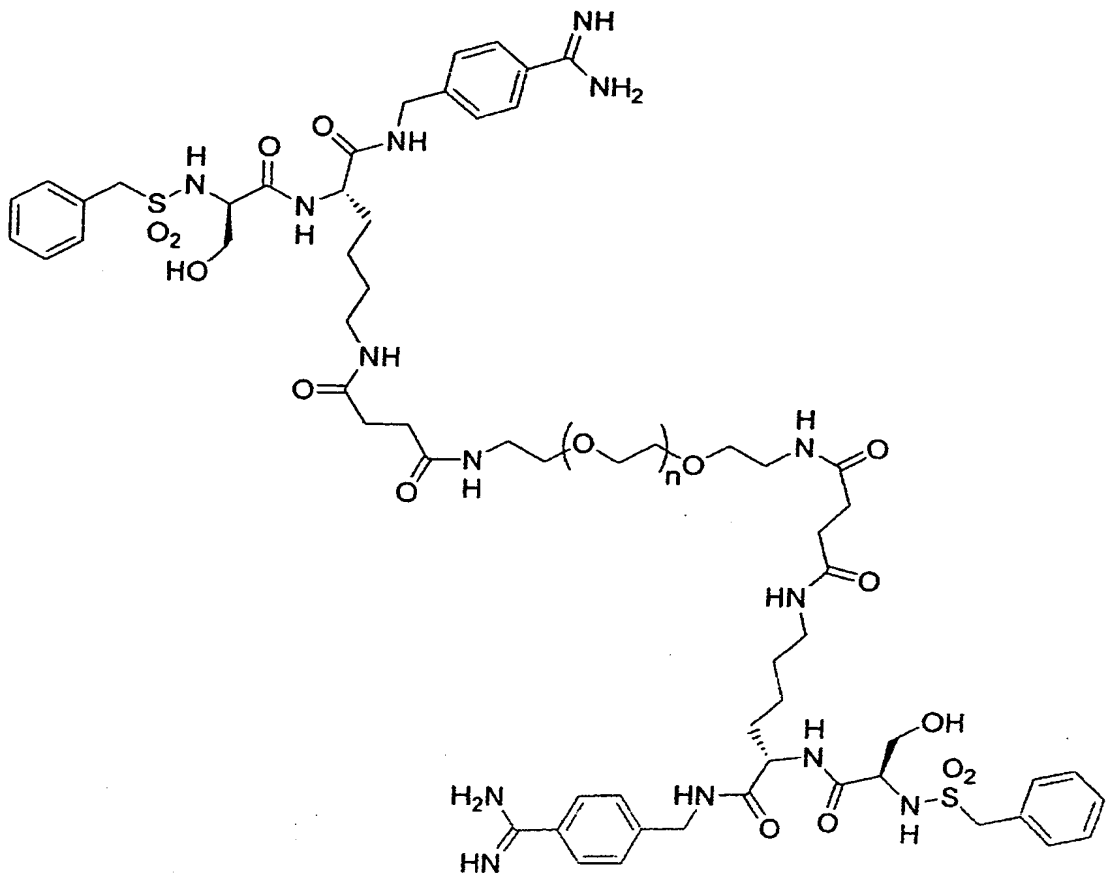

in which n = 2 to 250.

14. A compound as claimed in claim 1, characterized in that the compounds are preferably present as salts, preferably with mineral acids, preferably as hydrochloride, or preferably as salts with suitable organic acids.

15. A compound as claimed in claim 14, characterized in that preferred salts of mineral acids are also sulfates and suitable organic acids are, for example, acetic acid, formic acid, methylsulfonic acid, succinic acid, malic acid or trifluoroacetic acid, with preferred salts of organic acids being acetates.

16. A process for preparing a compound as claimed in claim 1, characterized in that the appropriate amino acids are sequentially coupled to a 4-acetyloxamidinobenzylamine, with either the N-terminal amino acid already carrying the R_5 radical or with this radical subsequently being bonded to it.

17. A pharmaceutical which comprises a compound as claimed in claim 1 and also pharmaceutically suitable auxiliary substances and/or additives.

18. A pharmaceutical as claimed in claim 17, wherein the pharmaceutical is used in the form of a tablet, of a sugar-coated tablet, of a capsule, of a pellet, of a suppository, of a solution, in particular of an injection solution or infusion solution, of eyedrops, nose drops and ear drops, of a juice, of an emulsion or suspension, of a globule, of a stylus, of an aerosol, of a powder, of a paste, of a cream or of an ointment.

19. A method of treating or preventing a tumor, in particular for reducing the formation of tumor metastases, said method comprising administering to a patient a compound as claimed in claim 1, preferably in oral, subcutaneous, intravenous or transdermal form.